FKTN gene

fukutin

Normal Function

The *FKTN* gene (formerly known as FCMD) provides instructions for making a protein called fukutin. This protein is present in many of the body's tissues but is particularly abundant in heart (cardiac) muscle, the brain, and the muscles used for movement (skeletal muscles). Within cells, fukutin is found in a specialized structure called the Golgi apparatus, where newly produced proteins are modified.

The fukutin protein is involved in a protein modification process called glycosylation. Through this chemical process, sugar molecules are added to certain proteins. In particular, the fukutin protein adds a molecule called ribitol 5-phosphate to the chain of sugars attached to a protein called alpha (α)-dystroglycan. Glycosylation is critical for the normal function of α-dystroglycan.

The α-dystroglycan protein helps anchor the structural framework inside each cell (cytoskeleton) to the lattice of proteins and other molecules outside the cell (extracellular matrix). In skeletal muscles, glycosylated α-dystroglycan helps stabilize and protect muscle fibers. In the brain, it helps direct the movement (migration) of nerve cells (neurons) during early development.

Health Conditions Related to Genetic Changes

Fukuyama congenital muscular dystrophy

At least 18 mutations in the *FKTN* gene have been found to cause Fukuyama congenital muscular dystrophy, a condition that causes skeletal muscle weakness and brain and eye abnormalities. This form of congenital muscular dystrophy is seen almost exclusively in Japan. Virtually everyone with this condition has at least one copy of the same mutation, an insertion of about 3,000 extra DNA building blocks (3 kilobases [kb]) in the *FKTN* gene. This insertion occurs in a part of the gene known as the 3' untranslated region, which helps regulate the gene's activity. Researchers believe that the 3-kb insertion reduces the amount of fukutin protein that is produced from the gene.

A shortage of fukutin prevents the normal glycosylation of α-dystroglycan. As a result, α-dystroglycan can no longer effectively anchor cells to the proteins and other molecules that surround them. Without functional α-dystroglycan to stabilize the

muscle fibers, they become damaged as they repeatedly contract and relax with use. The damaged fibers weaken and die over time, which affects the development, structure, and function of skeletal muscles in people with Fukuyama congenital muscular dystrophy.

Defective α-dystroglycan also affects the migration of neurons during the early development of the brain. Instead of stopping when they reach their intended destinations, some neurons migrate past the surface of the brain into the fluid-filled space that surrounds it. Researchers believe that this problem with neuronal migration causes a brain abnormality called cobblestone lissencephaly, in which the surface of the brain lacks the normal folds and grooves and instead appears bumpy and irregular. Less is known about the effects of *FKTN* mutations in other parts of the body.

limb-girdle muscular dystrophy

Walker-Warburg syndrome

At least 11 *FKTN* gene mutations have been identified in people with Walker-Warburg syndrome, the most severe form of congenital muscular dystrophy. This condition is found in populations worldwide. Like Fukuyama congenital muscular dystrophy (described above), Walker-Warburg syndrome is associated with skeletal muscle weakness and eye and brain abnormalities, including cobblestone lissencephaly; however, individuals with Walker-Warburg syndrome have more severe brain and eye abnormalities and live only into infancy or early childhood. The *FKTN* gene mutations associated with this condition prevent the production of any functional fukutin protein, which leads to the severe muscle, eye, and brain problems that develop in Walker-Warburg syndrome.

other disorders

Mutations in the *FKTN* gene cause other disorders that affect skeletal muscles and the heart. Unlike Fukuyama congenital muscular dystrophy (described above), which is mostly limited to the Japanese population, these conditions have been described in several populations worldwide.

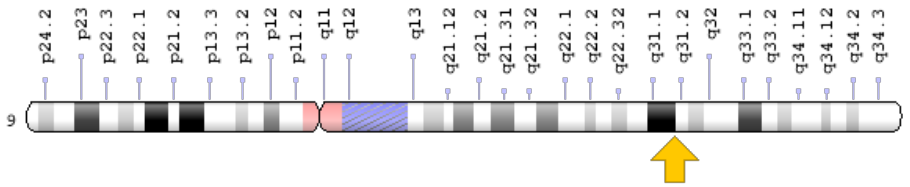
Several people with a heart condition called dilated cardiomyopathy have been found to have mutations in the *FKTN* gene. This condition weakens and enlarges the heart, preventing it from pumping blood efficiently. When dilated cardiomyopathy is associated with *FKTN* gene mutations, it is known as type 1X (DCM1X). In addition to heart problems, some people with DCM1X have experienced mild skeletal muscle weakness beginning in adulthood.

Changes in the *FKTN* gene that reduce but do not eliminate the production of fukutin lead to the somewhat less severe medical problems seen in DCM1X and limb-girdle muscular dystrophy (linked above).

Chromosomal Location

Cytogenetic Location: 9q31.2, which is the long (q) arm of chromosome 9 at position 31.2

Molecular Location: base pairs 105,558,117 to 105,655,950 on chromosome 9 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- CMD1X
- FCMD
- FKTN_HUMAN
- Fukuyama type congenital muscular dystrophy protein
- LGMD2M
- MGC126857
- MGC134944
- MGC134945
- MGC138243

Additional Information & Resources

Educational Resources

- Molecular Cell Biology (fourth edition, 2000): Protein Glycosylation in the ER and Golgi Complex
  https://www.ncbi.nlm.nih.gov/books/NBK21744/
- Neuromuscular Disease Center, Washington University
  http://neuromuscular.wustl.edu/syncm.html#fukuyama

GeneReviews

- Congenital Muscular Dystrophy Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1291
- Dilated Cardiomyopathy Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1309
- Fukuyama Congenital Muscular Dystrophy
  https://www.ncbi.nlm.nih.gov/books/NBK1206
- Limb-Girdle Muscular Dystrophy Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1408

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28FKTN%5BTIAB%5D%29+OR+%28fukutin%5BTIAB%5D%29+OR+%28FCMD%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- CARDIOMYOPATHY, DILATED, 1X
  http://omim.org/entry/611615
- FUKUTIN
  http://omim.org/entry/607440

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_FKTN.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=FKTN%5Bgene%5D
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=3622
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/2218
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  http://www.uniprot.org/uniprot/O75072

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